REMARKS

Claims 8-22 are currently pending. Claims 8-22 have been rejected.

Specification Objection under 35 U.S.C. §132

With respect to "calibrators and cellular RNA," the Examiner contends that new matter was introduced by the previous amendments. Applicants respectfully disagree with the Examiner's contention.

The Examiner points to the applicants' previous arguments of pointing to page 22, lines 1-3 for support as "a discussion of a step performed in Example 3, while the objection pertains to steps taken during a different example, Example 4...[and]cannot provide basis for modifying the method steps of Example 4" (Office Action- page 3). Applicants respectfully disagree with the Examiner's contention.

As the Examiner well knows, one need not teach, and preferably omits, that which is well known in the art. One skilled in the art would understand that the calibrators are used to create a calibration curve for quantifying HPV mRNA. Standard curves are commonly used in the art in order to quantify an unknown sample. Applicants have simply clarified the description in Example 4 in order to conform with the language of Example 3. However, in order to expedite prosecution of the instant application, applicants have cancelled the objected subject matter by amending the specification at page 23, line 11 to page 24, line 2. Reconsideration and withdrawal of this §132 objection is respectfully requested.

Claim Rejections under 35 U.S.C. §112

Claims 8-12 and claims 13-22 are rejected under 35 U.S.C. §112, first paragraph as containing subject matter which allegedly does not enable one skilled in the art how to make and use the invention. More particularly, the Examiner contends that the instant application and data presented in the Declaration do not enable the claims because there is allegedly a lack of correlation between HPV16 and any other HPV type; and the amount of experimentation needed to practice the claimed invention is allegedly undue. Applicants respectfully disagree with this rejection.

Most recently, in a case entitled *Invitrogen v. Clontech* (Slip Opinion 04-1039, -1040, Nov. 18, 2005), the Federal Circuit addressed the enablement requirement, stating "the enablement requirement is met if the description enables any mode of making and using the invention." In addition, the Federal Circuit stated that §112 requirements will vary depending upon "the nature and scope of [an] invention" and the "scientific and technologic knowledge already in existence" (*Capon v. Eshhar* 418 F.3d 1349, 1357 (Fed. Cir. 2005)). Specifically, the court stated that enablement is determined with respect to the state of knowledge in the field and differences in the predictability of the science at issue. (*Id.*)

The state of the knowledge in the HPV field has been shown in the Lorincz Declaration. Applicants respectfully submit that this declaration and the references discussed in it provide an overview of the state of knowledge in this field. In his declaration, Dr. Lorincz states that the prior art reference by Koromilas, et. al. describes "high risk HPV types 16, 18, 31, 33, 35, 39, and 41-45" as the infectious agents in cervical neoplasia. (Lorincz Declaration, p. 5.) One skilled in the art understands from this description that HPV16 is representative of the high-risk HPVs. In fact, this reference also sets forth the correlation that these types of HPV provide the viral genes such as E6 and E7 that are "critical for the development of malignant transformation and also play a role in altering the cellular response to cytokines." (Lorincz Declaration, pp. 5-6 (citing Koromilas, et. al., p. 158, col. 1, par. 2).) In the pending Office Action, the Examiner asserts that the cited prior art references do not show changes in the ratios of various genes. While it is true that these prior art references do not establish these ratios (if they did, the invention would not be novel), the data provided in the specification and the declaration advance the prior art to show the ratios in three separate HPV types – this is the invention as is claimed. Indeed, what the references demonstrate is that one skilled in the art recognizes that different HPV strains have similar expression patterns. Having this background, the skilled artisan would understand that the claimed invention is not limited to a single strain of HPV, but can be readily used for other strains upon reading the instant application. Thus, the references discussed in the Lorincz declaration demonstrate the level of knowledge in the field.

Regarding "predictability of the science", the Federal Circuit has stated that "the law must take cognizance of the scientific facts" (*Capon v. Eshhar,* 418 F.3d 1349, 1357 (Fed. Cir. 2005)) or in other words, the Examiner must consider that which is already known in the field in determining just how "unpredictable" the science is. In the field of HPV, it is clear from

the references discussed in the Lorincz declaration that the skilled artisan recognizes that the high risk HPV strains have similar gene expression characteristics. Thus, the teachings of the instant application can be readily converted to use in any HPV strain. No undue experimentation is necessary. "Enablement does not require the inventor to foresee every means of implementing an invention at pains of losing his patent franchise." *Invitrogen Corp. v. Clontech Labs, Inc.*, (*Slip Op.* 04/1039, -1040 at 29, Nov. 18, 2005)

The Federal Circuit has also stated that "[i]t is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art." (*In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991).) In addition, it is established law that "[t]he fact that some experimentation is necessary does not preclude enablement as long as the amount of experimentation is reasonable given the nature of the invention and the state of the art. (*Boston Scientific Scimed, Inc. v. Cordis Corp.*, 2005 U.S. Dist. LEXIS 23612 (D. Del., October 14, 2005 at *13).)

The Examiner has taken the position that there is allegedly a "lack of guidance in the specification and in the prior art with respect to diagnosis and/or monitoring of cancer in a patient by determination of the HPV gene transcript ratios of the claims." Applicants respectfully disagree.

The specification provides a method of correlating a specific HPV gene expression ratio to a disease state. One skilled in the art can readily adopt this method for any HPV strain without any undue experimentation. In addition, applicants have provided several prior art references that recognize a correlation between HPV16 and other high risk HPV types so that one of ordinary skill in the art would be able to use the information contained within the specification to make or use the claimed invention. Additionally, the Lorincz Declaration provides data showing that the method described in the specification relating to HPV16 also applies to other high risk HPVs, HPV18 and HPV31. (Lorincz Declaration, pp. 7-12.) These data illustrate the application of the invention to other types of HPV "to determine disease level in cell model systems of HPV-infected cells." (*Id.* at 12.) A generic claim is enabled as long as the "disclosure teaches those skilled in the art what the invention is and how to practice it." (*In re Grimme*, 124 USPQ at 502.) Thus, the skilled artisan can readily practice the invention with any HPV species by following the teachings of the instant application in view of his awareness of the knowledge in the HPV field.

The Examiner also contends that the declaration does not sufficiently establish the ratios of the claims to particular types or stages of HPV diseases, other than for HPV16-induced diseases. The Examiner believes that the declaration only uses cultured cells and there is no correlation provided between these cultured cell types and the various stages of HPV-induced disease.

Applicants respectfully direct the Examiner's attention to the Lorincz declaration beginning at page 8, ¶30 which describes a method of determining the E6-E7/ L1 mRNA ratio in HeLa cells. These cells, derived from cervical cancer cells removed from a woman, represent a human cervical carcinoma cell line. The inventive method of diagnosing high risk or HPV-induced disease uses this cell line to determine the E6-E7/ L1 mRNA ratio which represents this specific disease stage. For example, Table 3 of the instant specification indicates the resulting 9.5 E6-E7/ L1 mRNA ratio which is greater than a E6 and/or E7 mRNA to L1 and/or L2 and/or E2 mRNA of 4, where this ratio is indicative of HPV18-induced cancer (see, for example, claim 16).

With respect to HPV 31, Table 7 of the instant specification shows the E6-E7/ L1 mRNA ratio of HPV 31 in two cell lines, LKP31 and A31. Human keratinocytes were transfected with varying copies of HPV 31 DNA. Specifically, LKP31 had a higher copy number than A31, and represents a cell line closer to HPV-induced cancer stage. Similar to Hela cells, LKP31 and A31 represent the HPV-induced cancer stage of disease.

The resulting ratios for both HPV 18 and HPV 31 have E6-E7/ L1 mRNA ratios greater than 2 and greater than 4 which correspond to the HPV-induced disease stages. The cell lines that are used in these experiments represent *in vivo* conditions, and as the Examiner is well aware, "[u]se of *in vitro* experiments to establish *in vivo* events is, in principle, a valid methodology." *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985); *Nelson v. Bowler*, 626 F.2d 853, 856, 206 U.S.P.Q. 881 (C.C.P.A. 1980). Therefore, the high risk HPV types exemplified in the instant specification and the Lorincz declaration provide a guide for one skilled in the art who recognizes that different high risk HPV strains have similar expression patterns.

In summary, the Federal Circuit stated that "[i]t is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic

invention." (*Capon,* 418 F.3d at 1359.) In the case at hand the inventors have presented general teachings of how to identify HPV diseases in patient samples and also specific examples of the identification using *in vitro* models identifying HPV16-induced disease. Given the knowledge within the field as shown in the cited prior art references, one skilled in the art would be able to use the information provided in the specification to make and use the claimed invention without undue experimentation. Reconsideration and withdrawal of this §112, first paragraph rejection is respectfully requested.

CONCLUSION

Based on the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

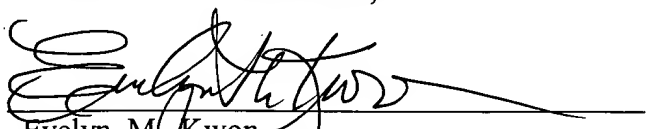
AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **13-4500**, Order No. 2629-4005US4. A DUPLICATE OF THIS DOCUMENT IS ATTACHED.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **13-4500**, Order No. 2629-4005US4. A DUPLICATE OF THIS DOCUMENT IS ATTACHED.

Respectfully submitted,
MORGAN & FINNEGAN, L.L.P.

Dated: November 23, 2005

By: 
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